PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X15830	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/032771	International filing date *(day/month/year)* 28.10.2004	Priority date *(day/month/year)* 10.11.2003
International Patent Classification (IPC) or national classification and IPC C07D265/30, C07D413/06, A61K31/5375, A61K31/5377, A61P25/22		
Applicant ELI LILLY AND COMPANY		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 12 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.08.2005	17.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Stix-Malaun, E Telephone No. +49 89 2399-8057

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/032771

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-114 as originally filed

   Claims, Numbers

   1-33 received on 14.09.2005 with letter of 12.09.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27,28

because:

☒ the said international application, or the said claims Nos. 27,28 (Industrial Applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-33
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26,29-33
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

III NON-ESTABLISHMENT

Claims 27,28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Functional definitions such as "protecting group" are not clear (see claims 29-32);

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: WO 03/018576 A (ASTRAZENECA AB; GUSTAFSSON, JOERGEN; HOSSAIN, NAFIZAL; NILSSON, STINAB) 6 March 2003 (2003-03-06)

D2: WO 01/00214 A (MERCK & CO., INC; HUNT, JULIANNE, A; MILLS, SANDER, G; SINCLAIR, PETER) 4 January 2001 (2001-01-04)

D3: KING, FRANK D. ET AL: "The synthesis of 2-morpholinecarboxylic acid derivatives and their elaboration to 1-aza-4-oxabicyclo[3.3.1]nonan-6-one" TETRAHEDRON LETTERS , 32(20), 2281-4 CODEN: TELEAY; ISSN: 0040-4039, 1991, XP002317574

D4: WO 01/01973 A (PHARMACIA & UPJOHN COMPANY; WONG, ERIK, H., F; AHMED, SAEEDUDDIN; MARS) 11 January 2001 (2001-01-11)

D5: WO 99/37305 A (GLAXO GROUP LIMITED; MORGAN, PHILLIP, FREDERICK; MUSSO, DAVID, LEE; PA) 29 July 1999 (1999-07-29)

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 31 and 32 is novel on account of the specific definition of the variable R1.

The claimed subject-matter of the remaining claims is considered to be novel .The essential structural difference between the claimed compounds and those of the prior art resides in the presence of the specific substituent in position 2 of the morpholine unit (Article 33(2) PCT).

3. INVENTIVE STEP

The subject-matter of the novel claims appears to fulfil the requirements of Article 33(3) PCT for the following reasons:

The closest state of the art for the present application is represented by D4 and D5. Said documents deal with reuptake inhibitors. The compounds of D4 and D5 differ as explained under item novelty.

The problem of the present application may be seen in the provision of further substituted morpholines acting as norepinephrine reuptake inhibitors,and which are therefore useful in the treatment of diseases/disorders such as anxiety and hyperactivity

Neither D4 or D5 nor the combination of the two teach the structural variation necessary in order to arrive at the presently claimed compounds.

Accordingly the presently claimed solution does not appear to be obvious.
It is proofed in the description the problem is actually solved. In a regional phase it might become necessary to indicate at least one tested compound in order to allow an assessment of the plausibility of the generalisation of claim 1.

The novel intermediates contribute structurally to the products.

Accordingly inventive step can in principle be acknowledged.

VI CERTAIN DOCUMENTS CITED

D6: FR-A-2 852 954 (AVENTIS PHARMA SA) 1 October 2004 (2004-10-01)

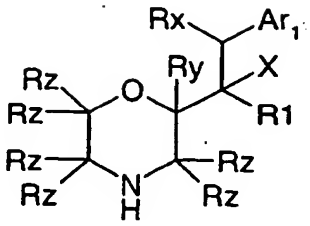
D7: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KATO, SHIRO ET AL: "1-(1-Substituted-4-piperidinylmethyl)piperidine derivatives as 5-TH4 receptor agonists, pharmaceutical compositions containing them, and their use" XP002317575 retrieved from STN Database accession no. 2004:819908

D8: WO 2004/018441 A (ELI LILLY AND COMPANY; CASES-THOMAS, MANUEL, JAVIER; HAUGHTON, HELEN,) 4 March 2004 (2004-03-04)

D6-D8 might become highly relevant documents in the regional phase.

CLAIMS

1. A compound of formula (I)



(I)

wherein,

X is OH, C1-C4 alkoxy, NH_2 or NH(C1-C4 alkyl);

Rx is H or C1-C4 alkyl;

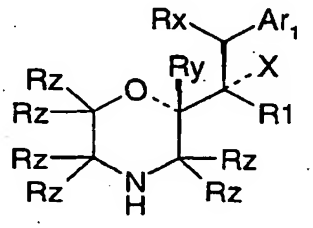
Ry is H or C1-C4 alkyl;

each Rz group is independently H or C1-C4 alkyl, with the proviso that not more than 3 Rz groups may be C1-C4 alkyl;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C2-C6 alkenyl (optionally substituted with 1, 2 or 3 halogen atoms); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; C4-C7 cycloalkylalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH_2Ar2; and Ar1 and Ar2 are each independently a phenyl ring or a 5- or 6-membered heteroaryl ring each of which is optionally substituted with 1, 2 or 3 substituents (depending upon the number of available substitution positions) each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1,

2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy and/or with 1 substituent selected from pyridyl, thiophenyl, phenyl, benzyl and phenoxy each of which is optionally ring-substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R; and each R is independently H or C1-C4 alkyl;
or a pharmaceutically acceptable salt thereof.

2. A compound of formula (II)



(II)

wherein, X, Rx, Ry, Rz, R1 and Ar1 are as defined for formula (I) in claim 1; or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in any preceding claim or claim 30 wherein X is OH.

4. A compound as claimed in any preceding claim or claim 30 wherein Rx is H.

5. A compound as claimed in any preceding claim or claim 30 wherein Ry is H.

6. A compound as claimed in any preceding claim or claim 30 wherein each Rz is H.

7. A compound as claimed in any one of claims 1 to 6 or 30 wherein R1 is C1-C6 alkyl optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-

C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy.

8. A compound as claimed in any one of claims 1 to 6 or 30 wherein R1 is C2-C6 alkenyl optionally substituted with 1, 2 or 3 halogen atoms.

9. A compound as claimed in any one of claims 1 to 6 or 30 wherein R1 is C3-C6 cycloalkyl optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond.

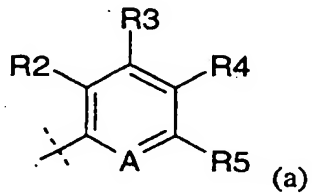
10. A compound as claimed in any one of claims 1 to 6 or 30 wherein R1 is C4-C7 cycloalkylalkyl optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond.

11. A compound as claimed in any one of claims 1 to 6 or 30 wherein R1 is CH_2Ar2 wherein Ar2 is a phenyl ring or a 5- or 6-membered heteroaryl ring each of which is optionally substituted with 1, 2 or 3 substituents (depending upon the number of available substitution positions) each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy and/or with 1 substituent selected from pyridyl, thiophenyl, phenyl, benzyl and phenoxy each of which is optionally ring-substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R.

12. A compound as claimed in any preceding claim or claim 30 wherein Ar1 is a phenyl ring or a 5- or 6-membered heteroaryl ring; each of which is substituted in the

ortho position with a substituent selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo, hydroxy, pyridyl, thiophenyl, phenyl, benzyl and phenoxy, each of which *ortho* substituents is optionally ring-substituted (where a ring is present) with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R; and each of which is (in addition to *ortho* substitution) optionally further substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy.

13. A compound as claimed in any preceding claim or claim 30 wherein Ar1 is a group of the formula (a):



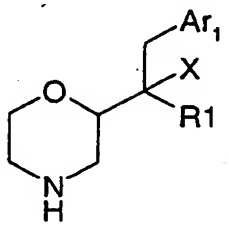
(a)

wherein,

A is N or CR6 (preferably CR6); R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo, hydroxy, pyridyl, thiophenyl, phenyl (optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), or C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms)) or phenoxy (optionally substituted with 1, 2 or 3 halogen atoms); R3 is H; R4 is H; R5 is H, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally

substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo or hydroxy; and R6 (if present) is H.

14. A compound of formula (III)



(III)

wherein, X, R1 and Ar1 are as defined for formula (I) in claim 1; or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 14 wherein

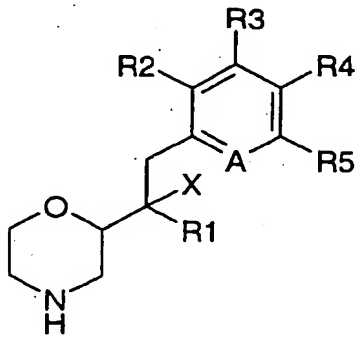
X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH_2Ar2 wherein Ar2 is a phenyl ring or a pyridyl (preferably 2-pyridyl) ring each of which may be substituted with 1, 2 or 3 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy; and

Ar1 is a phenyl ring or a 5- or 6-membered heteroaryl ring; each of which is substituted in the *ortho* position with a substituent selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -

CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo, hydroxy, pyridyl, thiophenyl, phenyl, benzyl and phenoxy, each of which *ortho* substituents is optionally ring-substituted (where a ring is present) with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R; and each of which is (in addition to *ortho* substitution) optionally further substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy; or a pharmaceutically acceptable salt thereof.

16. A compound of formula (IV)



(IV)

wherein,

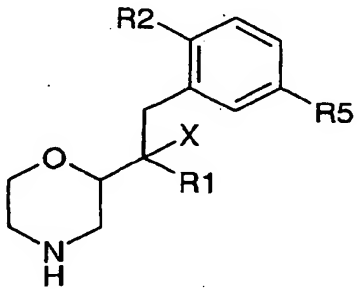
X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), cyano, and hydroxy); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond; or CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted with 1, 2 or 3 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1,

2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy;

A is N or CR6 (preferably CR6); R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo, hydroxy, pyridyl, thiophenyl, phenyl (optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), or C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms)) or phenoxy (optionally substituted with 1, 2 or 3 halogen atoms); R3 is H; R4 is H; R5 is H, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo or hydroxy; and R6 (if present) is H; or a pharmaceutically acceptable salt thereof.

17. A compound of formula (V)



(V)

wherein,

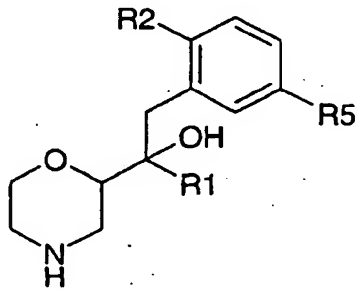
X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkyl wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond or CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1,

2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy;

R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms) or phenyl (optionally substituted with 1, 2 or 3 fluorine atoms); and R5 is H or F; or a pharmaceutically acceptable salt thereof.

18. A compound of formula (VI)



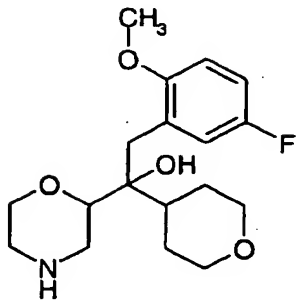
(VI)

wherein,

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms) or C3-C6 cycloalkyl wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond;

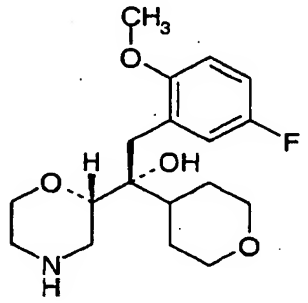
R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms) or phenyl (optionally substituted with 1, 2 or 3 fluorine atoms); and R5 is H or F; or a pharmaceutically acceptable salt thereof.

19. A compound of the formula



or a pharmaceutically acceptable salt thereof.

20. A compound of the formula



or a pharmaceutically acceptable salt thereof.

21. The hydrochloride salt, of a compound according to claim 19 or claim 20.

22. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 21, except when dependent upon claim 30, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent, excipient or carrier.

23. A compound as claimed in any one of claims 1 to 21, except when dependent upon claim 30, for use in therapy.

24. A compound as claimed in any one of claims 1 to 21, except when dependent upon claim 30, or pharmaceutically acceptable salt thereof for use as an inhibitor of the reuptake of norepinephrine.

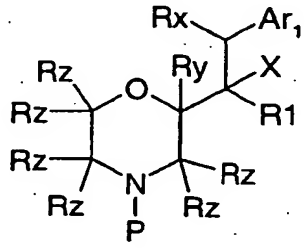
25. A compound as claimed in any one of claims 1 to 21, except when dependent upon claim 30, or a pharmaceutically acceptable salt thereof for treating disorders associated with norepinephrine dysfunction in mammals.

26. The use of a compound as claimed in any one of claims 1 to 21, except when dependent upon claim 30, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disorders associated with norepinephrine dysfunction in mammals.

27. A method for inhibiting the reuptake of norepinephrine in mammals comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 21, except when dependent upon claim 30, or a pharmaceutically acceptable salt thereof.

28. A method for treating disorders associated with norepinephrine dysfunction in mammals comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 21, except when dependent upon claim 30, or a pharmaceutically acceptable salt thereof.

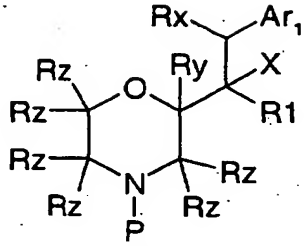
29. A process for the preparation of a compound of formula (I) comprising the step of deprotecting a compound of the formula (XIV)



(XIV)

wherein P represents an N-protecting group and all other variables are as defined for formula (I) in claim 1, to provide a compound of formula (I), optionally followed by the step of forming a pharmaceutically acceptable salt.

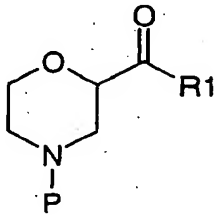
30. A compound of the formula (XIV)



(XIV)

wherein P represents an N-protecting group and all other variables are as defined for formula (I) in claim 1, or a salt thereof.

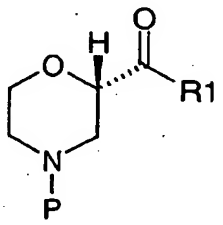
31. A compound of the formula (XIII)



(XIII)

wherein P represents an N-protecting group and R1 is a tetrahydro-2H-pyran-4-yl group, or a salt thereof.

32. A compound of the formula (XIII)b



(XIII)b

wherein P represents an N-protecting group and R1 is a tetrahydro-2H-pyran-4-yl group, or a salt thereof.

33. A compound according to any one of claims 30 to 32, or a salt thereof, wherein P is a benzyl group.